Homology Modeling and GPCR Drug Discovery with BioHPC

Peng Lian
Computer Scientist, BioHPC
June 23, 2021

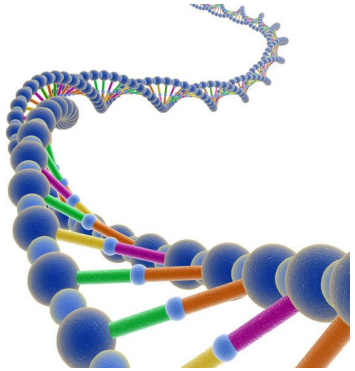
Outline

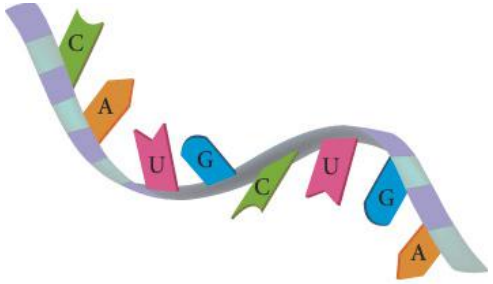
- Background on Biology, sequences, and structures

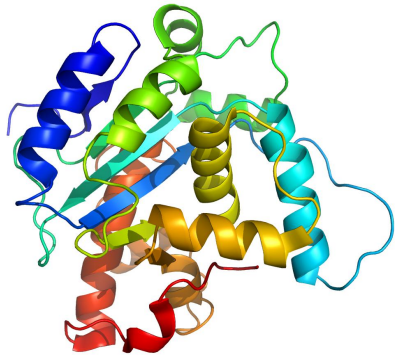
- Homology modeling
- Molecular docking

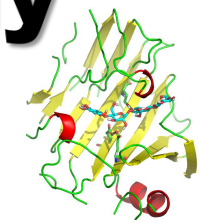
- GPCR as drug targets
- Hands-on Homology modeling of 5-HT_{1A} receptor
- Hands-on Molecular docking with Autodock on BioHPC
- Discussion on Virtual Screening

The Central Dogma of Biology

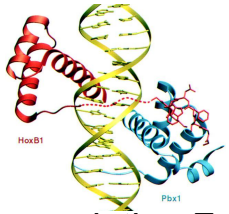




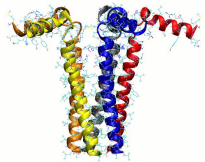




Enzymes



Transcription Factors



Signaling & Binding

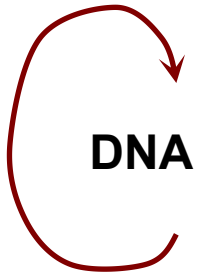
GPCR receptors

Kinases

Structural Proteins

……

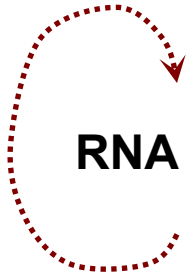
Functions



DNA

Transcription

Reverse Transcription



RNA

Translation

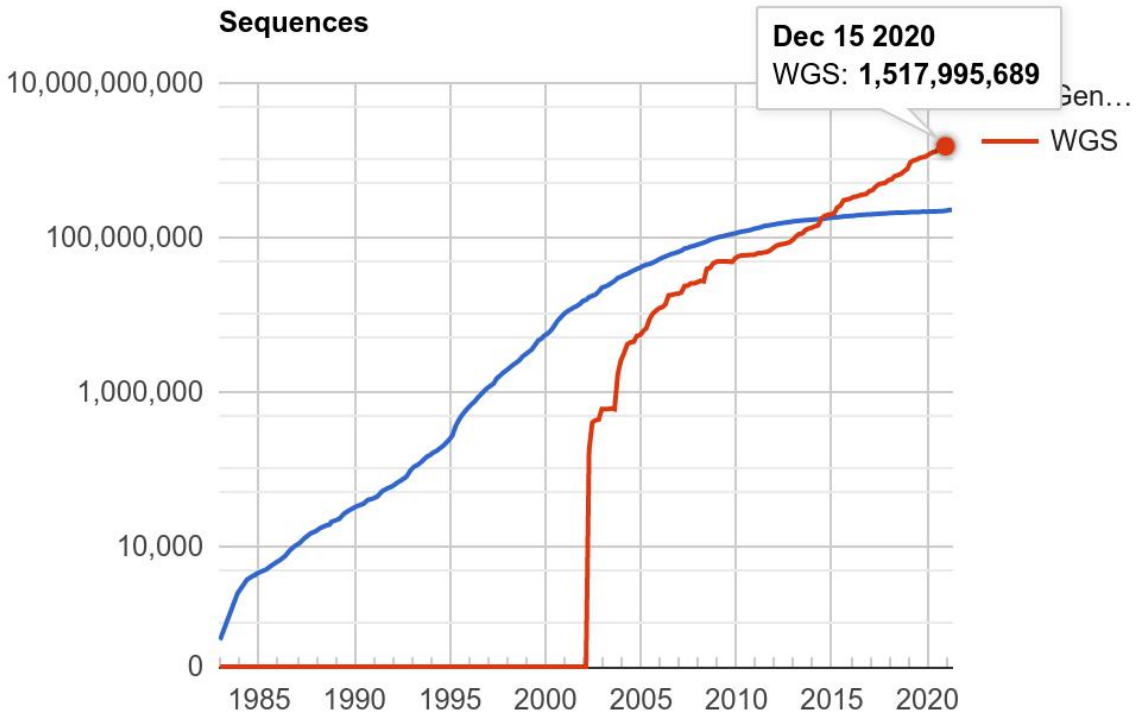
Protein

Replication

Replication

From Sequence to Structure

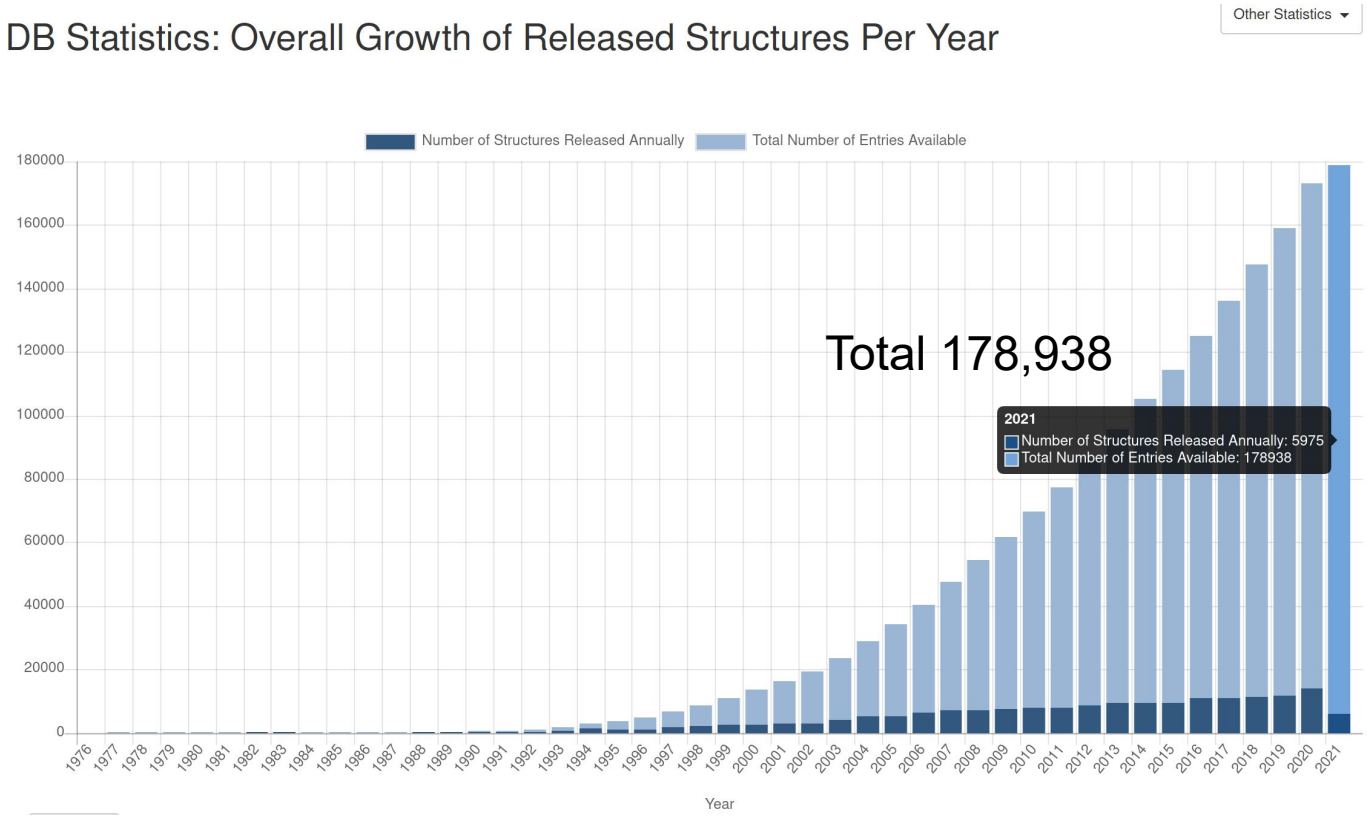
Sequence



GenBank

https://www.ncbi.nlm.nih.gov/genbank/statistics/

Structure

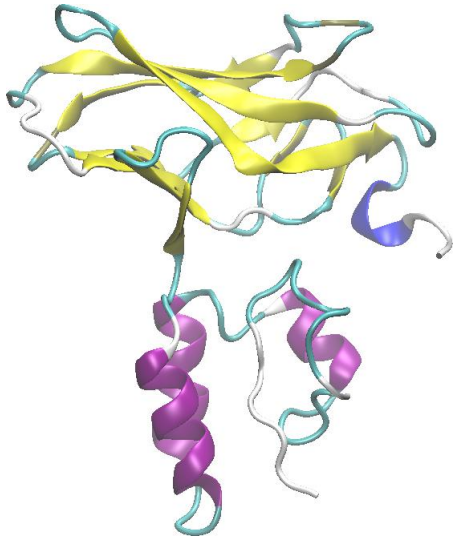


Protein Data Bank

https://www.rcsb.org/stats/growth/growth-released-structures

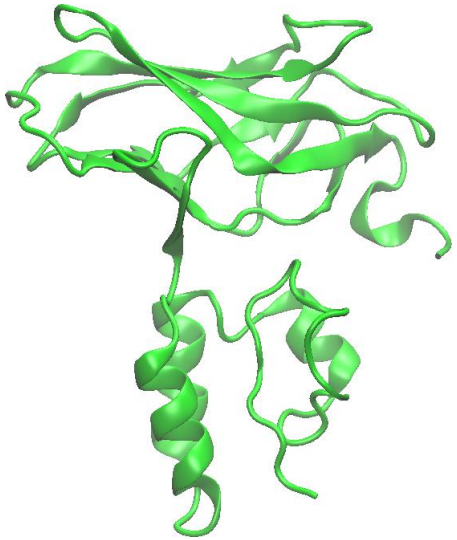
Homology Modeling

Template



Target

New Structure



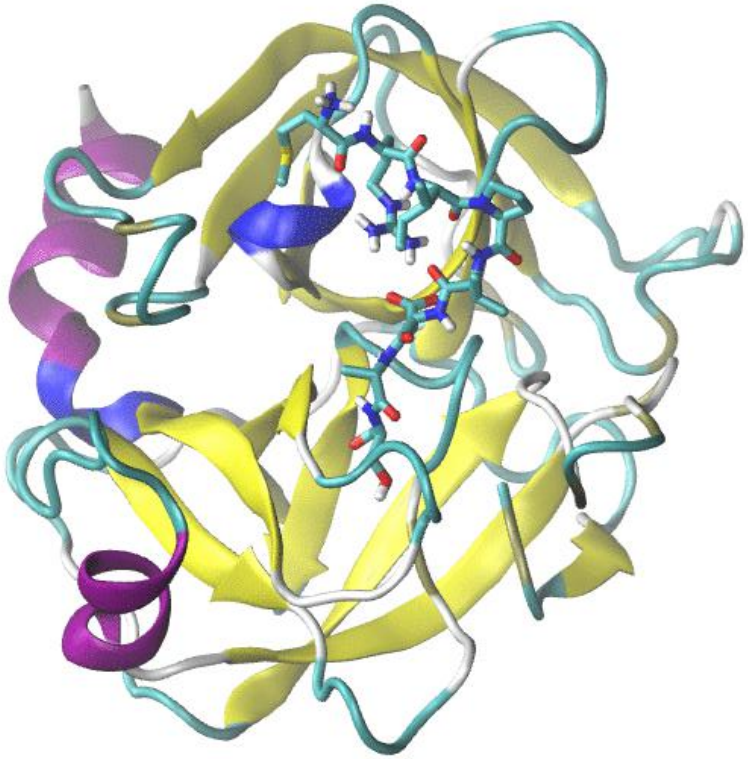
ELAGIILTVSYIPSAEKIA ELAIGILTVSYIPSAEKIR ELAIGILTVSYIPSAEKIR

Sequence Alignment

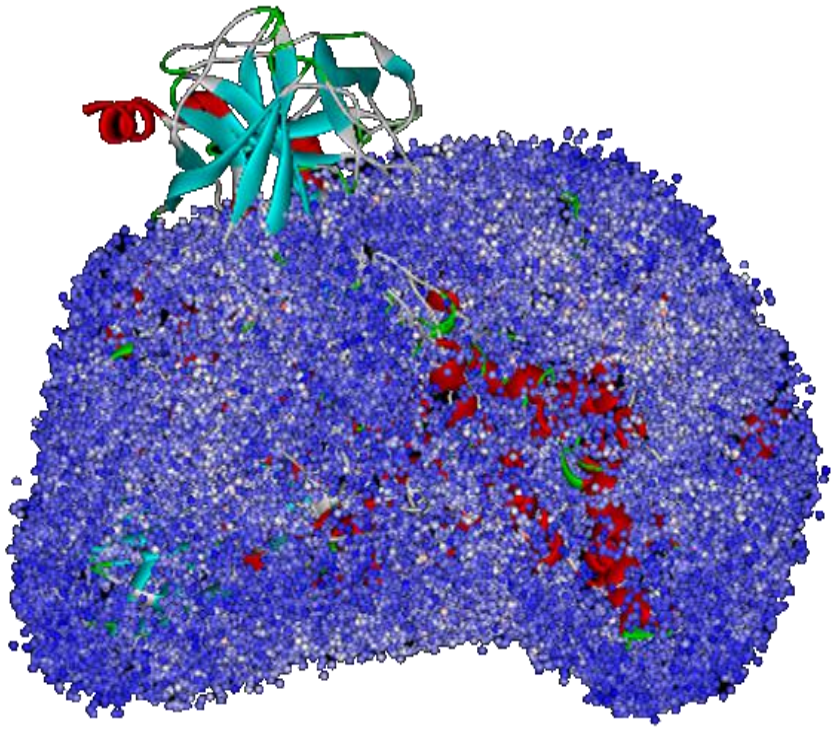
ELAGI-ILGVSYIPSAEKI-ARACELTI

ELA-IGILTVSYIPSAEKIRAR--ELTI

Molecular Docking

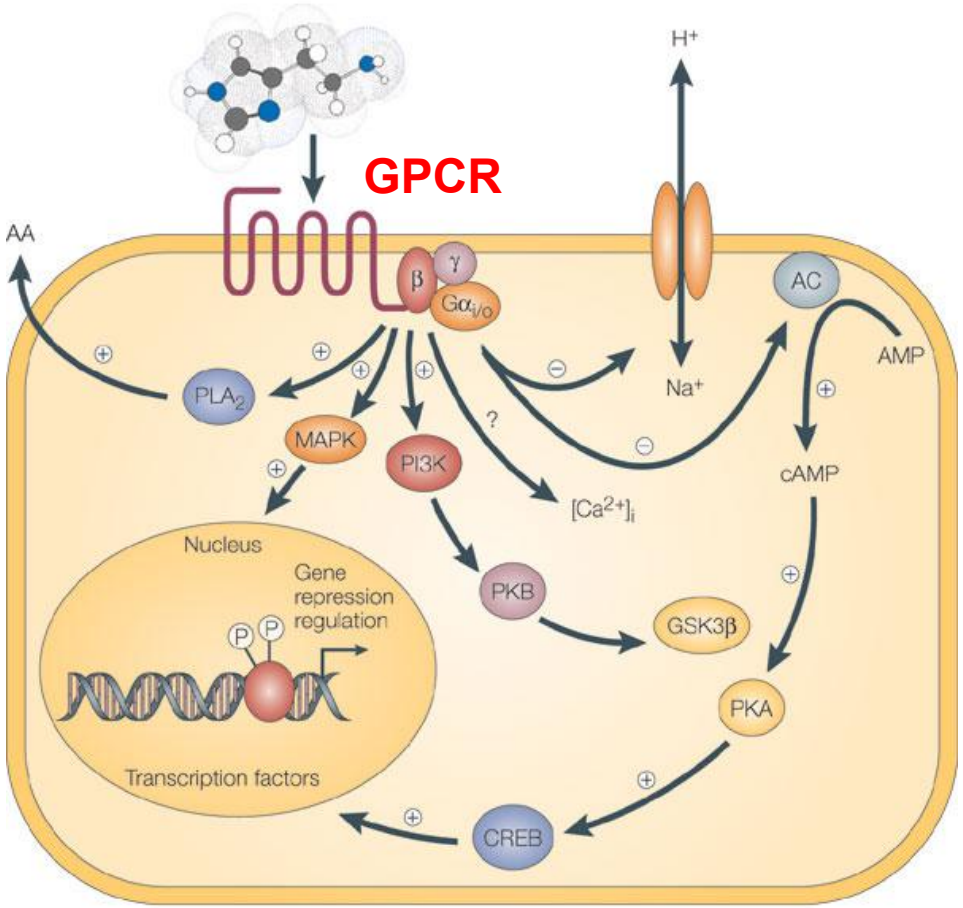


Small molecule Docking



Protein-Protein Docking

GPCR and Signaling Cascades

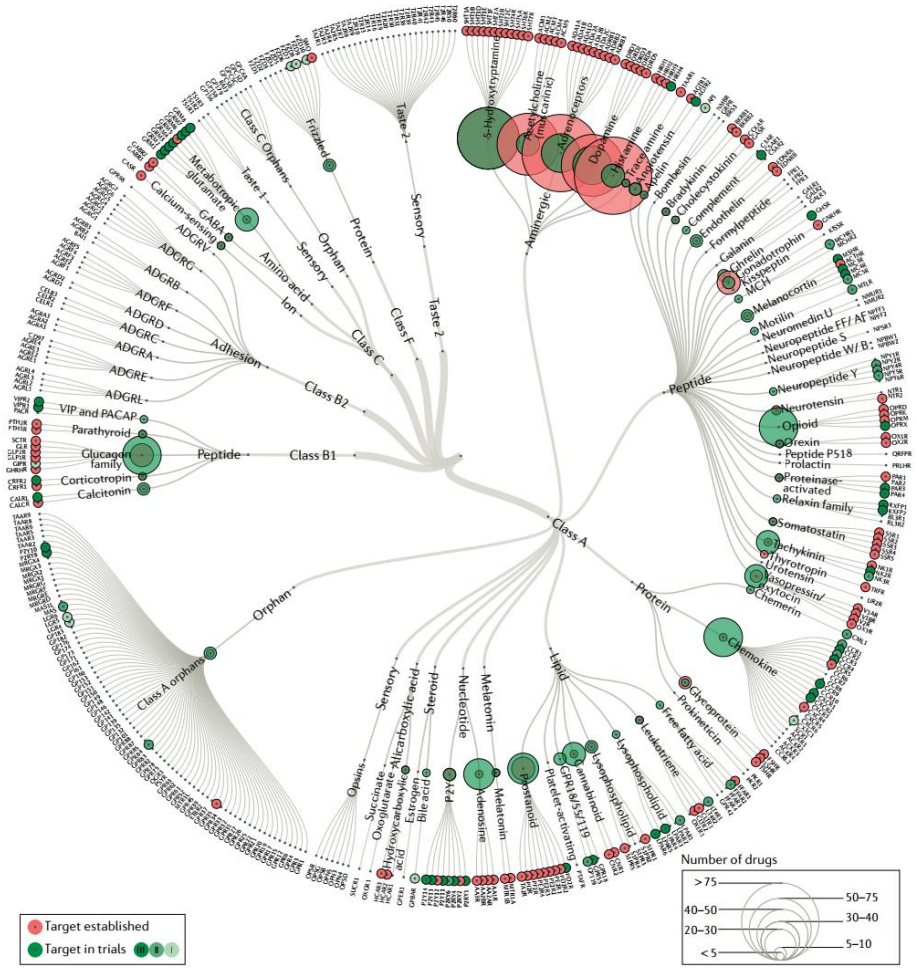


Nature Reviews | Drug Discovery

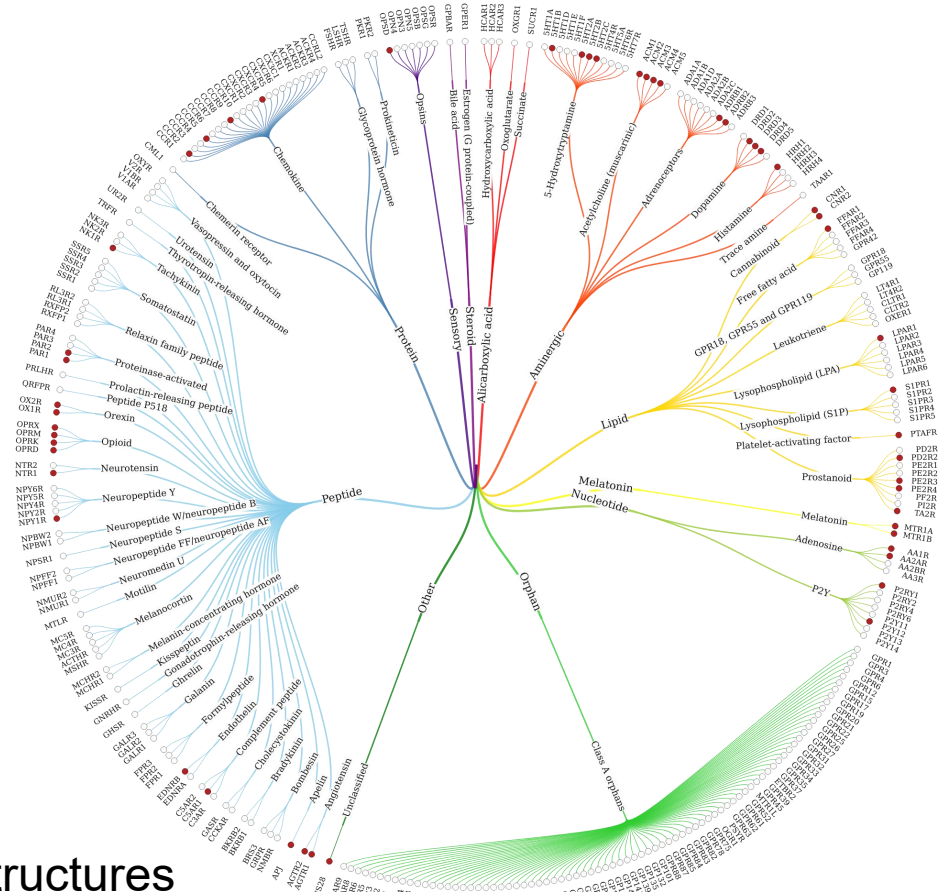
GPCR	Ligands
Active state	Agonists
Inactive state	Antagonists
Rest state	Inhibitors

https://www.nature.com/scitable/content/signaling-cascades-within-a-cell-can-interact-14673527/

GPCR as Drug Targets



475 FDA approved drugs (~34%) act on 108 unique GPCR targets. 321 are in clinical trail.



54 structures vs 800+ class A receptors

A. S. Hause, et al. *Nature Review*, 2017, vol 16, 829
https://gpcrdb.org/structure/statistics

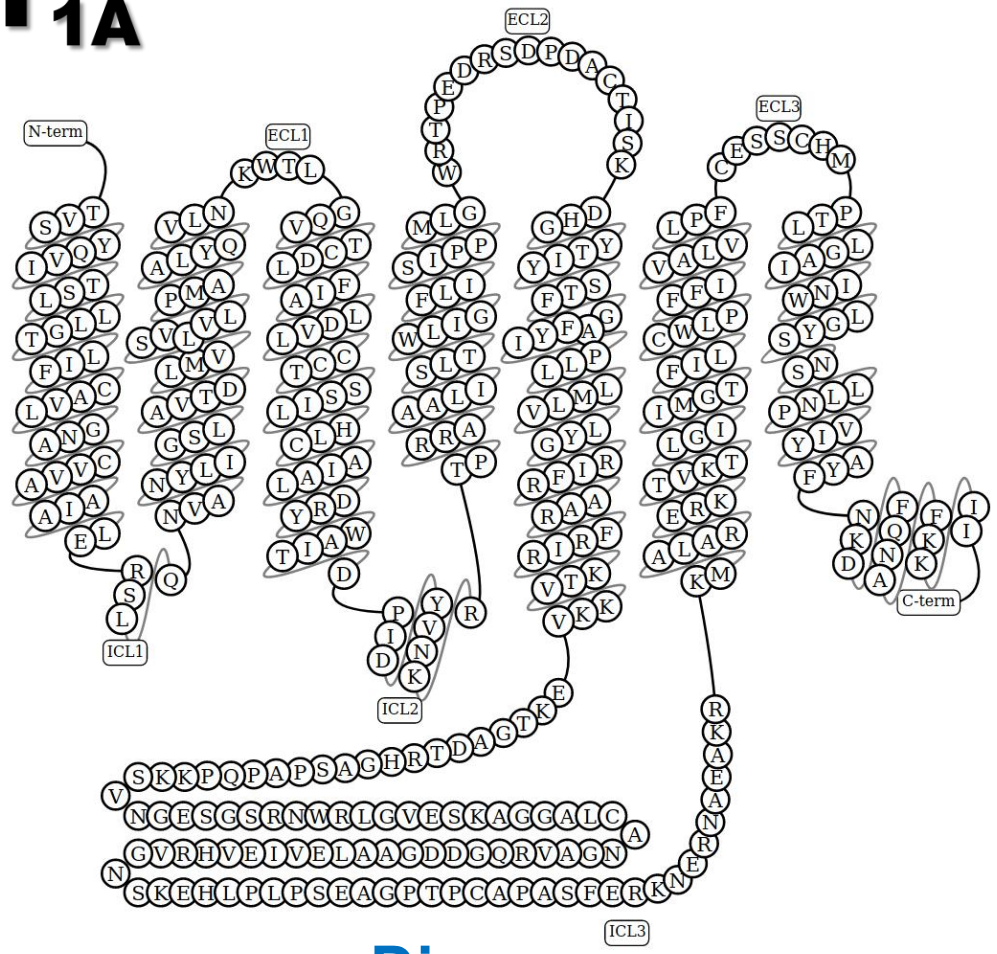
Serotonin Receptor 5-HT$_{1A}$

```
>sp|P08908|5HT1A_HUMAN 5-hydroxytryptamine receptor 1A
OS=Homo sapiens OX=9606 GN=HTR1A PE=1 SV=3
MDVLSPGQGNNTTSPPAPFETGGNTTGISDVTVSYQVITSLLLGTLIFCAVLGNACVVAA
IALERSLQNVANYLIGSLAVTDLMVSVLVLPMAALYQVLNKWTLGQVTCDLFIALDVLCC
TSSILHLCAIALDRYWAITDPIDYVNKRTPRRAAALISLTWLIGFLISIPPMLGWRTPED
RSDPDACTISKDHGYTIYSTFGAFYIPLLLMLVLYGRIFRAARFRIRKTVKKVEKTGADT
RHGASPAPQPKKSVNGESGSRNWRLGVESKAGGALCANGAVRQGDDGAALEVIEVHRVGN
SKEHLPLPSEAGPTPCAPASFERKNERNAEAKRKMALARERKTVKTLGIIMGTFILCWLP
FFIVALVLPFCESSCHMPTLLGAIINWLGYSNSLLNPVIYAYFNKDFQNAFKKIIKCKFC
RQ
```

Sequence

N-term			TM1		
MDVLSPGQGN	NTTSPPAPFE	TGGNTTGISD	VTVSYQVITS	LLLGTLIFCA	VLGNACVVAA
10	20	30	40	50	60
ICL1	TM2			ECL1 TM3	
IALERSLQNV	ANYLIGSLAV	TDLMVSVLVL	PMAALYQVLN	KWTLGQVTCD	LFIALDVLCC
70	80	90	100	110	120
		ICL2	TM4		ECL2
TSSILHLCAI	ALDRYWAITD	PIDYVNKRTP	RRAAALISLT	WLIGFLISIP	PMLGWRTPED
130	140	150	160	170	180
	TM5				ICL3
RSDPDACTIS	KDHGYTIYST	FGAFYIPLLL	MLVLYGRIFR	AARFRIRKTV	KKVEKTGADT
190	200	210	220	230	240
RHGASPAPQP	KKSVNGESGS	RNWRLGVESK	AGGALCANGA	VRQGDDGAAL	EVIEVHRVGN
250	260	270	280	290	300
			TM6		
SKEHLPLPSE	AGPTPCAPAS	FERKNERNAE	AKRKMALARE	RKTVKTLGII	MGTFILCWLP
310	320	330	340	350	360
	ECL3 TM7			H8	
FFIVALVLPF	CESSCHMPTL	LGAIINWLGY	SNSLLNPVIY	AYFNKDFQNA	FKKIIKCKFC
370	380	390	400	410	420
C-term					
R Q					

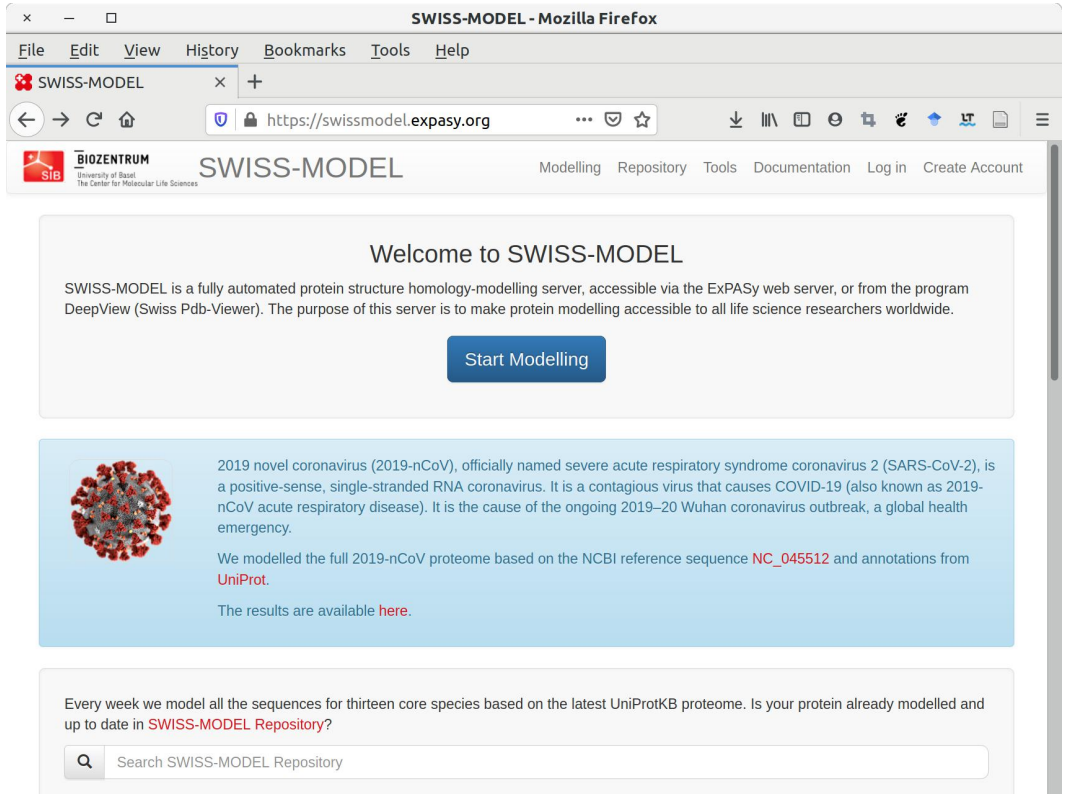
Domain Information

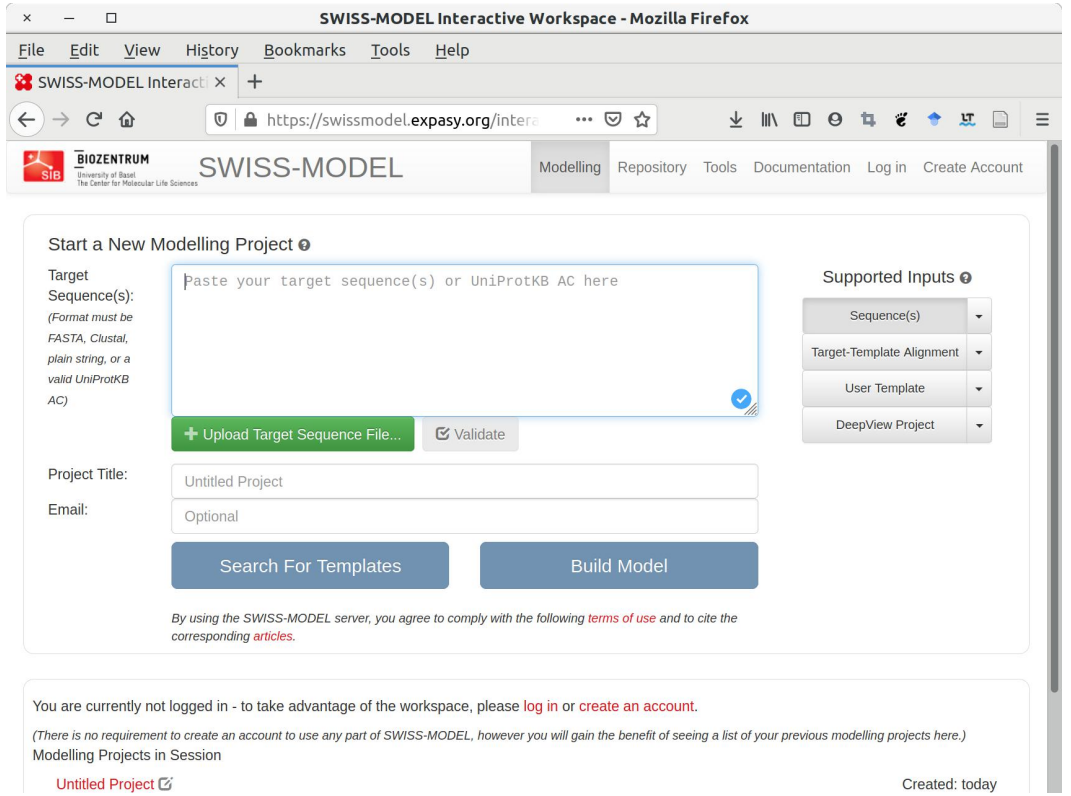


Diagram

But no 3D Structures yet!

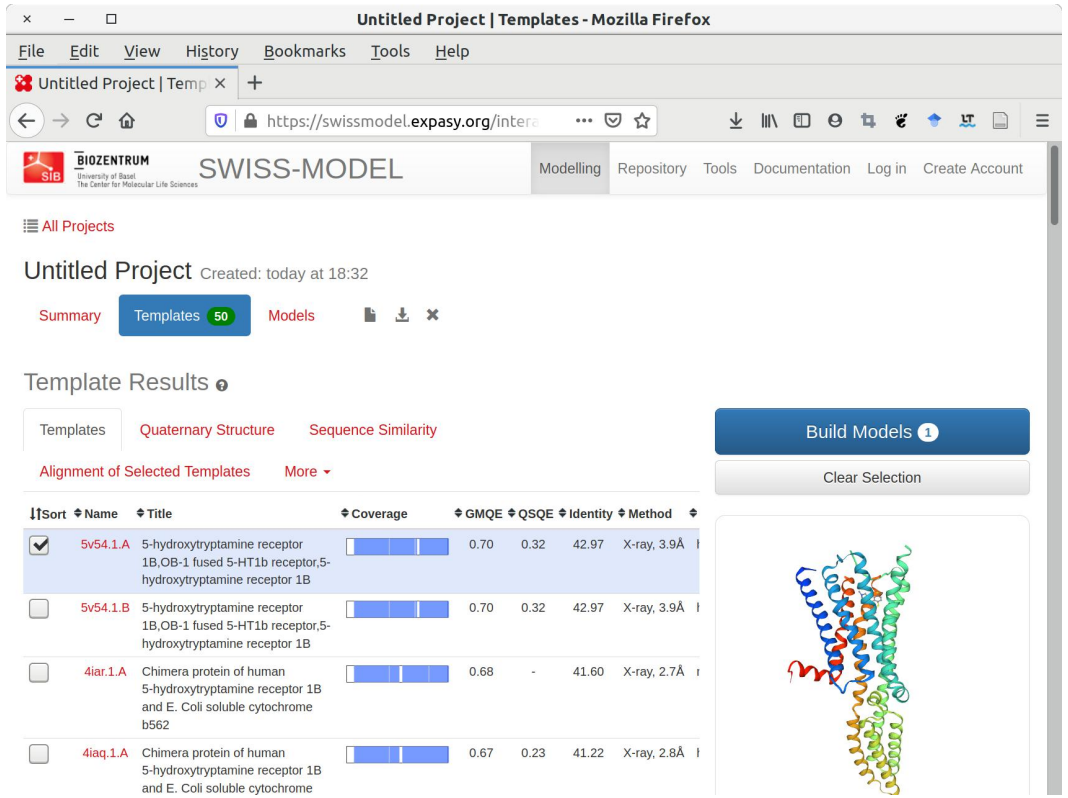
Build 3D Structure of 5-HT$_{1A}$ Receptor with Swiss-model

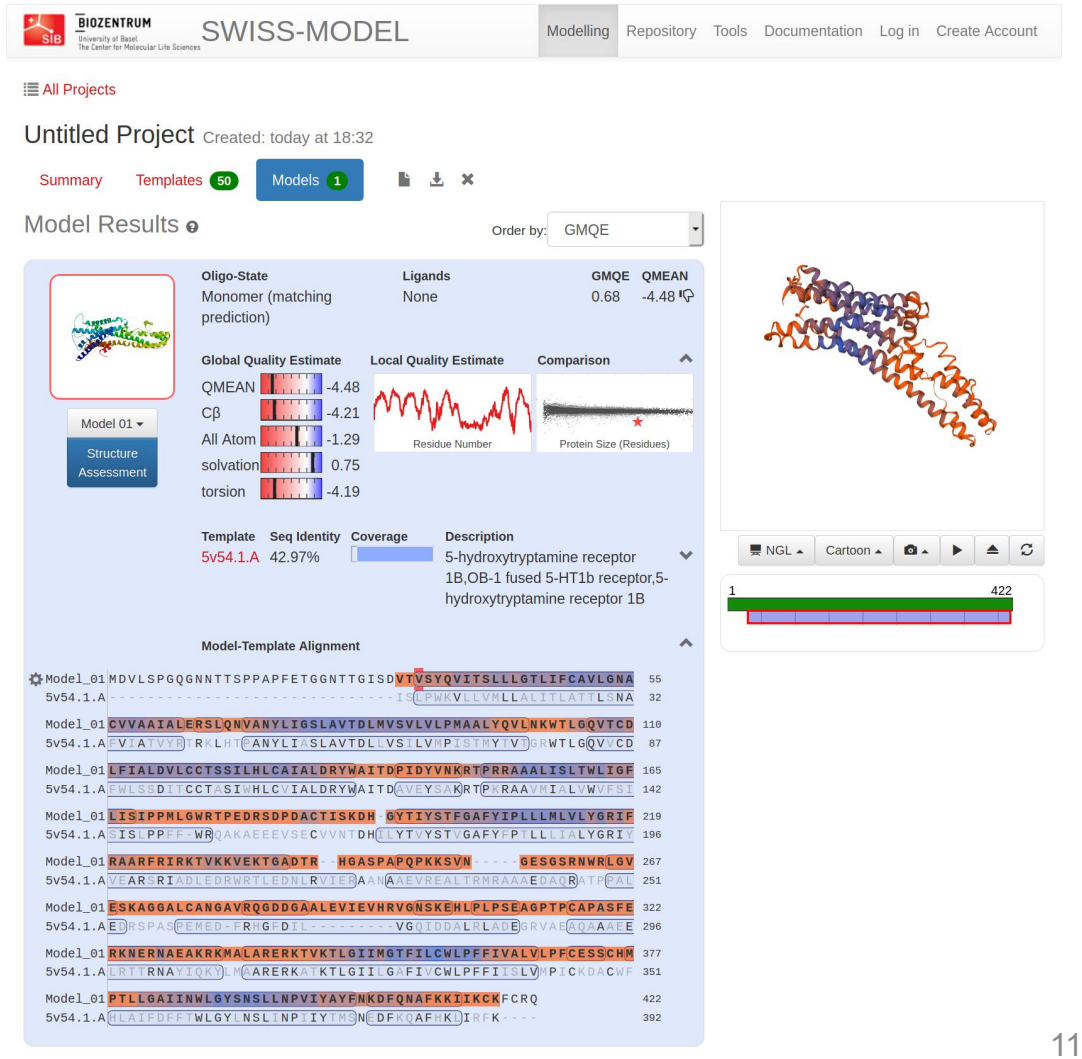




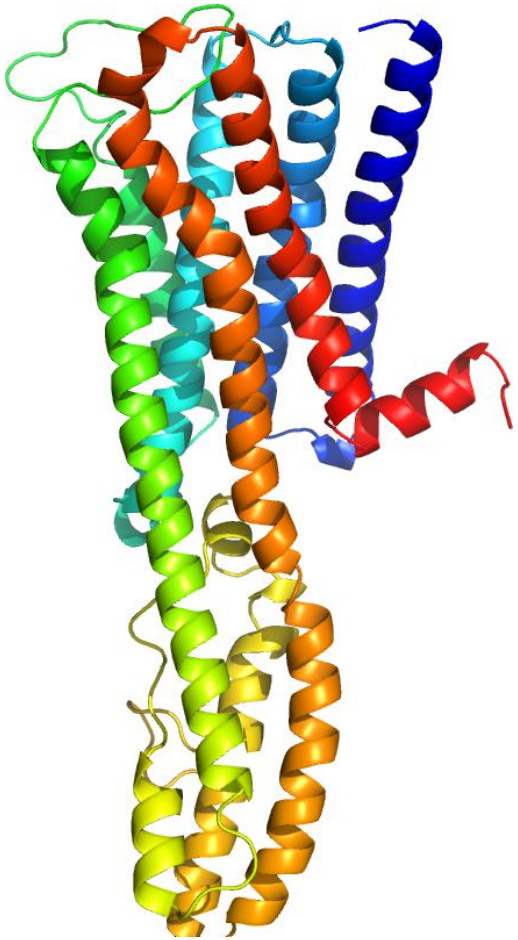
https://swissmodel.expasy.org/

Build 3D Structure of $5HT_{1A}$ Receptor with Swiss-model

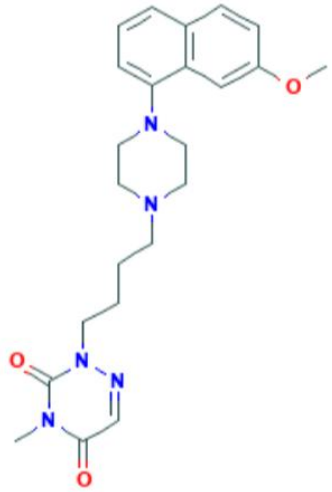




Molecular Docking with Autodock on BioHPC



Homology model of 5-HT_{1A} Receptor



PubChem ID: 10324985
EC50 with 5-HT_{1A}: 0.47 nM

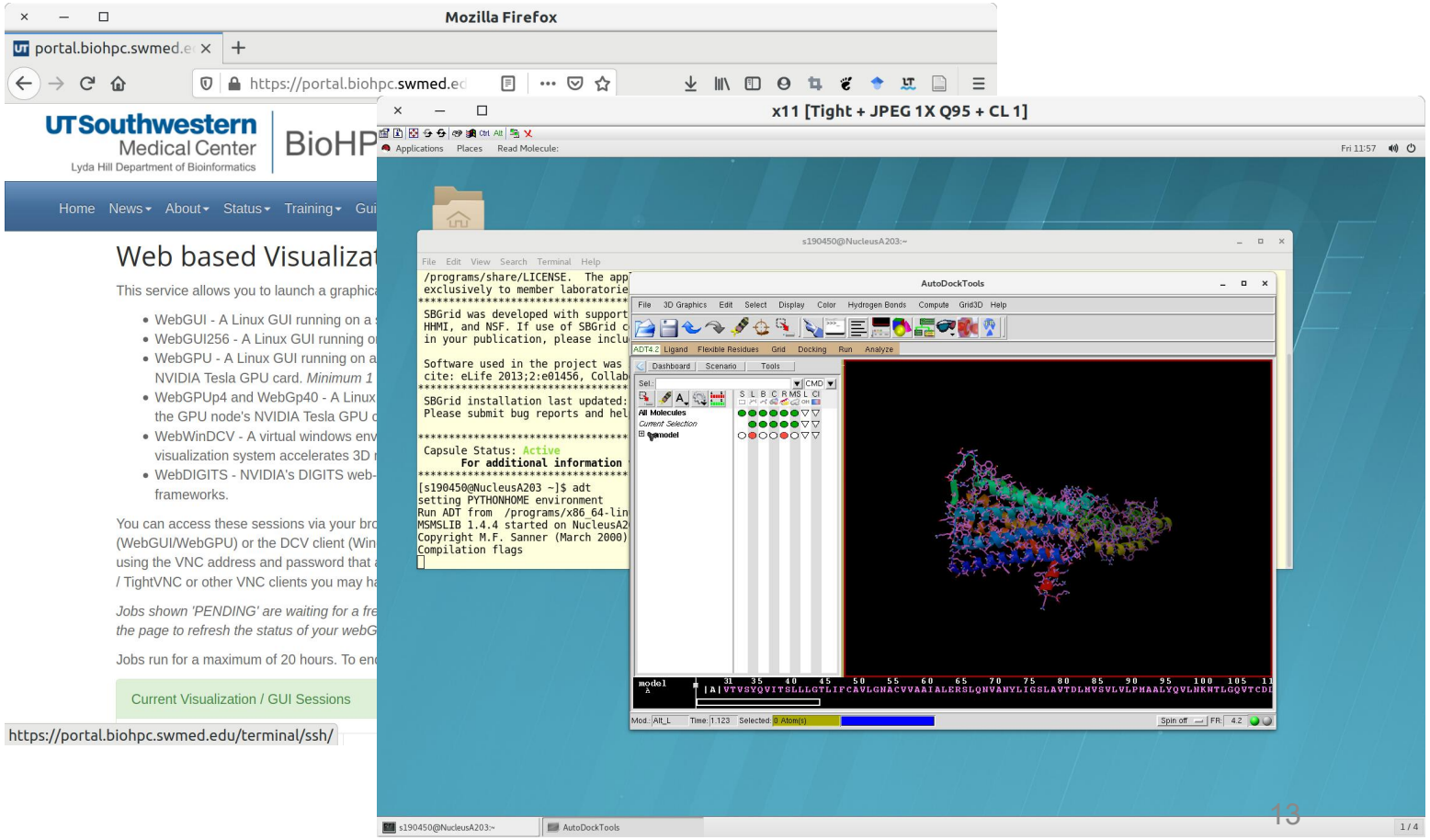
Molecular Docking with Autodock on BioHPC

`https://portal.biohpc.swmed.edu/`

-> Cloud Services

-> Web Visualization

-> VNC Viewer



Molecular Docking with Autodock on BioHPC

```
# Add sbgrid to your environment

vi .bashrc

. /programs/sbgrid.shrc

source .bashrc
```

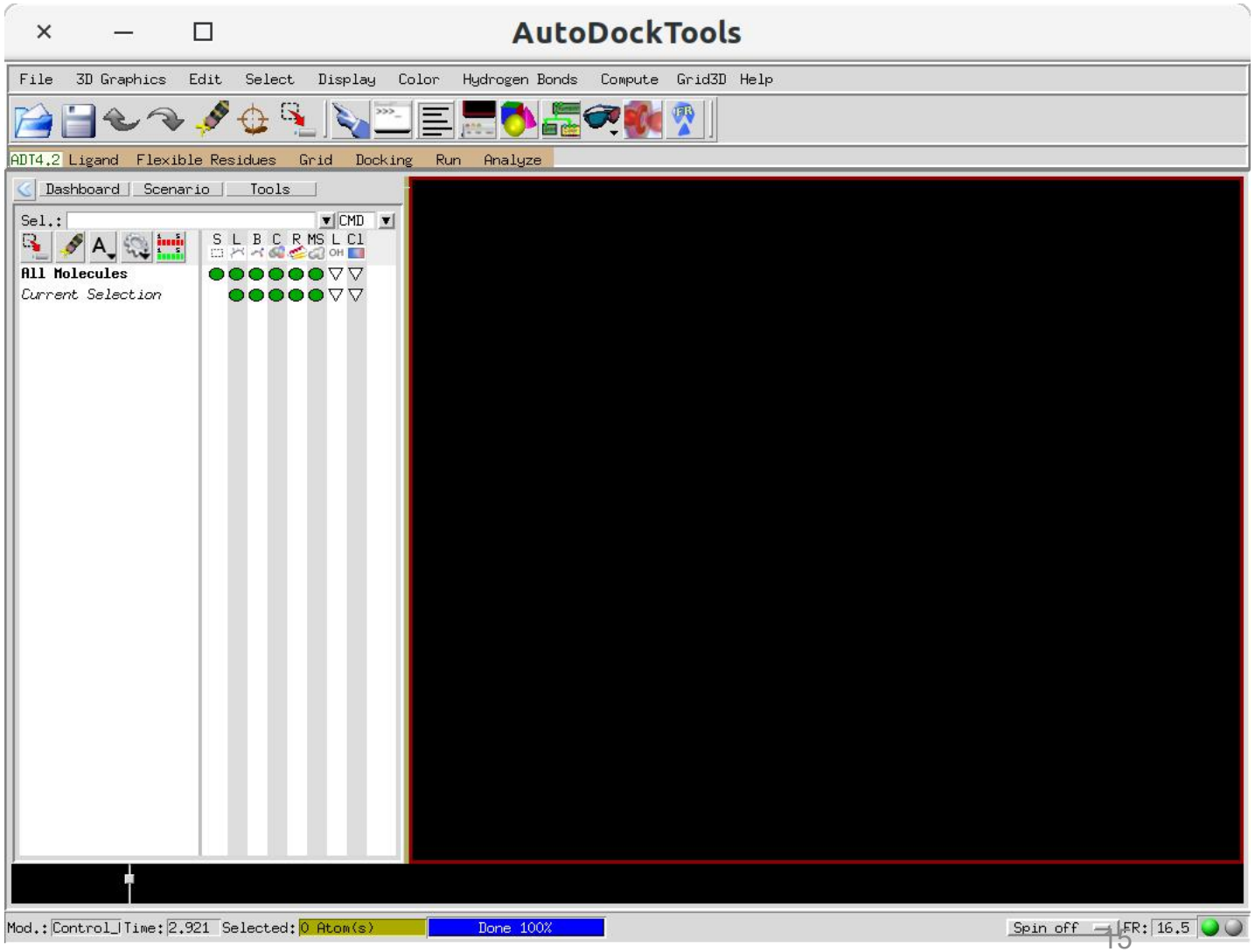
```
[s190450@Nucleus005 ~]$ vi .bashrc
[s190450@Nucleus005 ~]$ source .bashrc
********************************************************************************
                    Software Support by SBGrid (www.sbgrid.org)
********************************************************************************
                                SBGrid Announcements
- SBGrid is not compatible with MacOS 10.15 Catalina.
   see https://sbgrid.org/wiki/catalina for more info.
********************************************************************************
 Your use of the applications contained in the /programs  directory constitutes
 acceptance of  the terms of the SBGrid License Agreement included  in the file
 /programs/share/LICENSE.  The applications  distributed by SBGrid are licensed
 exclusively to member laboratories of the SBGrid Consortium.
********************************************************************************
 SBGrid was developed with support from its members, Harvard Medical School,
 HHMI, and NSF. If use of SBGrid compiled software was an important element
 in your publication, please include the following reference in your work:

 Software used in the project was installed and configured by SBGrid.
 cite: eLife 2013;2:e01456, Collaboration gets the most out of software.
********************************************************************************
 SBGrid installation last updated: in-progress (Update available)
 Please submit bug reports and help requests to:       <bugs@sbgrid.org>  or
                                                       <http://sbgrid.org/bugs>
********************************************************************************
 Capsule Status: Active
       For additional information visit https://sbgrid.org/wiki/capsules
********************************************************************************
[s190450@Nucleus005 ~]$
```

Molecular Docking with Autodock on BioHPC

```
# start Autodock Tools
```

```
adt
```



Molecular Docking with Autodock on BioHPC

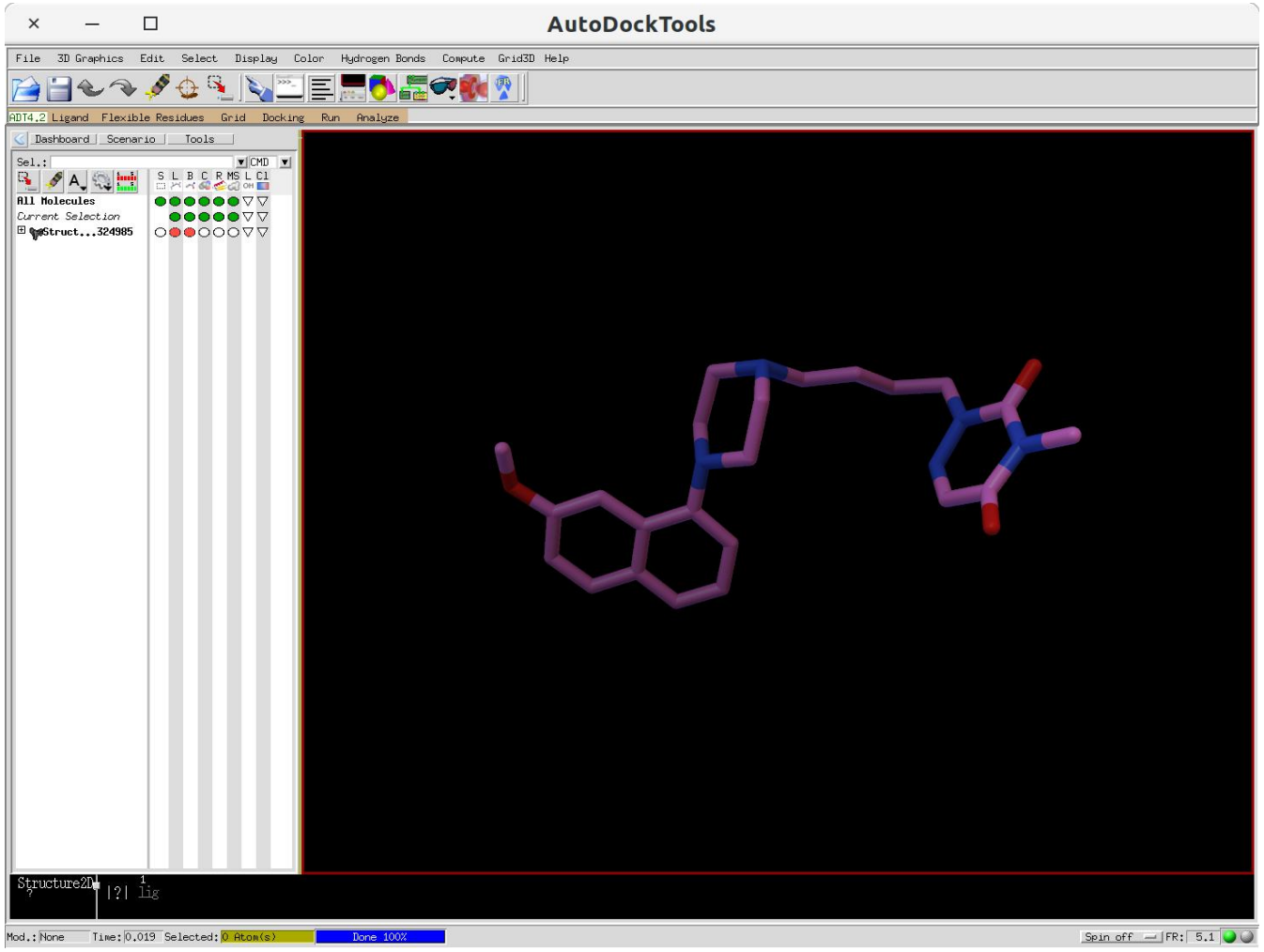
 # Prepare the ligand

Ligand -> Input -> Open -> lig.pdb

Ligand -> Torsion Tree -> Choose Torsions

Ligand -> Output -> Save as lig.pdbqt

Edit -> Delete -> Delete all Molecules



Molecular Docking with Autodock on BioHPC

 # Prepare the receptor

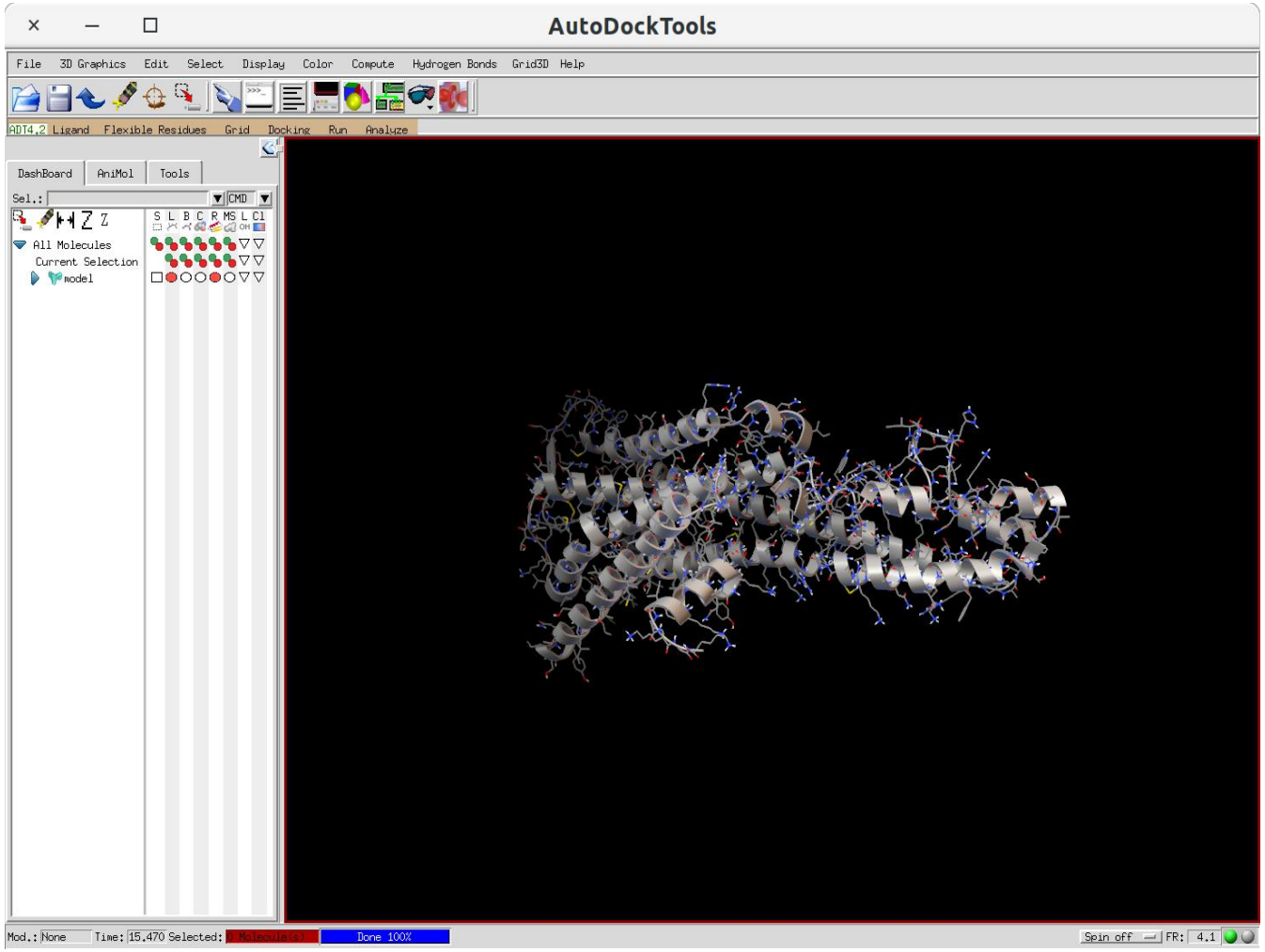
File-> Read Molecule -> model.pdb

Edit-> Hydrogens -> Add -> Polar only

Grid-> Macromolecule -> Choose ->

Save as model.pdbqt

Edit -> Delete -> Delete all Molecules



Molecular Docking with Autodock on BioHPC

 # Prepare the grids

Grid -> Macromolecule -> Open -> model.pdbqt

Grid -> Set Map Types -> Open ligand -> lig.pdbqt

Grid -> Grid Box -> (File -> Close saving current)

Grid -> Output -> box.gpf

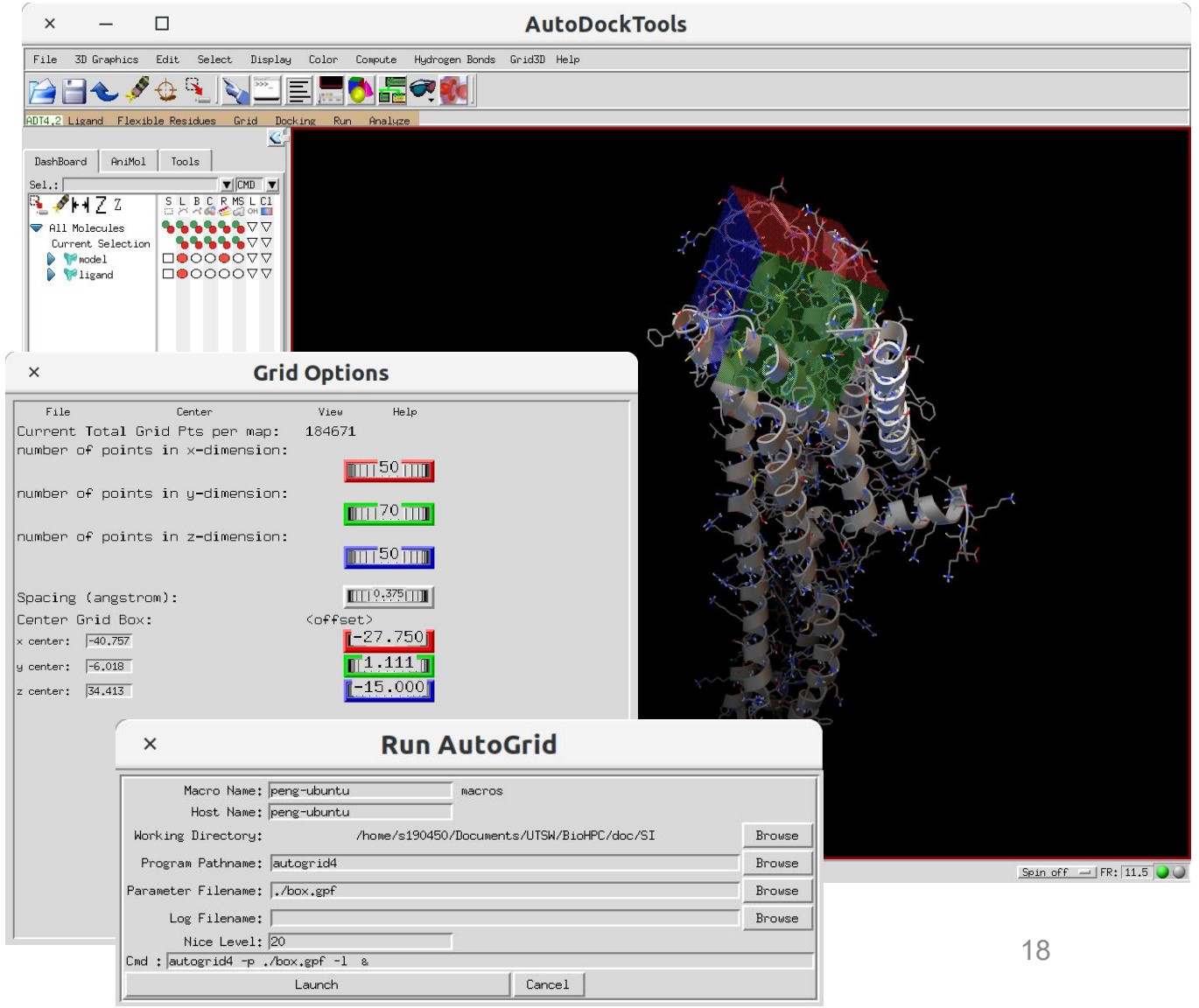
 # run autogrid4

autogrid4 -p box.gpf -l autogrid.log

(Run -> Run AutoGrid)

 # output files

model.A.map model.d.map
model.maps.fld model.NA.map
model.OA.map model.C.map
model.e.map model.maps.xyz
model.N.map



Molecular Docking with Autodock on BioHPC

 # Docking

Docking -> Macromolecule ->

Set Rigid Filename, rigid.pdbqt

Docking -> Ligand -> Open -> lig.pdbqt

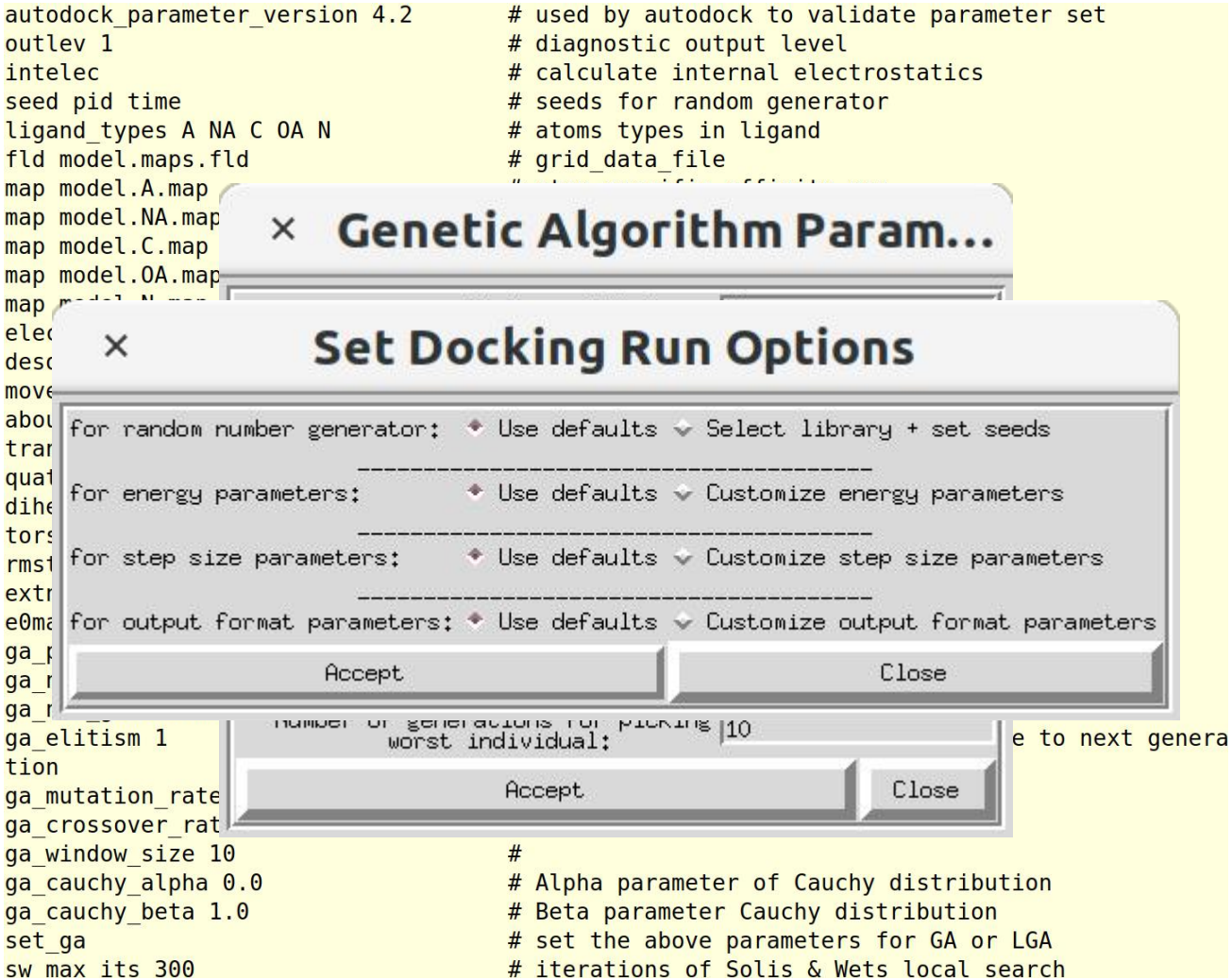
Docking -> Search Parameters -> Genetic Algorithm

Docking -> Docking Parameters

Docking -> Output -> Lamarckian GA(4.2) -> dock.dpf

autodock4 -p dock.dpf -l dock.dlg

(Run -> Run AutoDock)

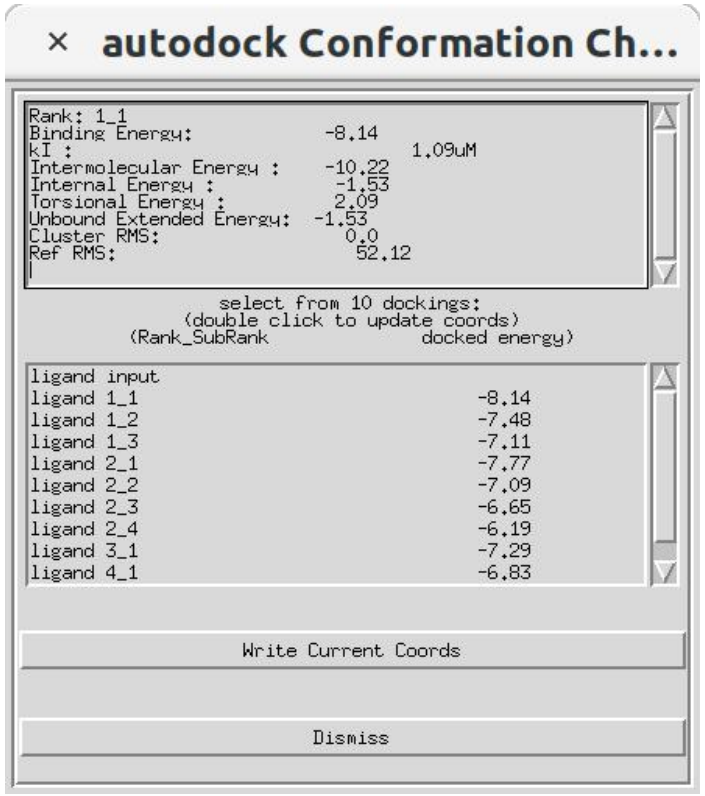


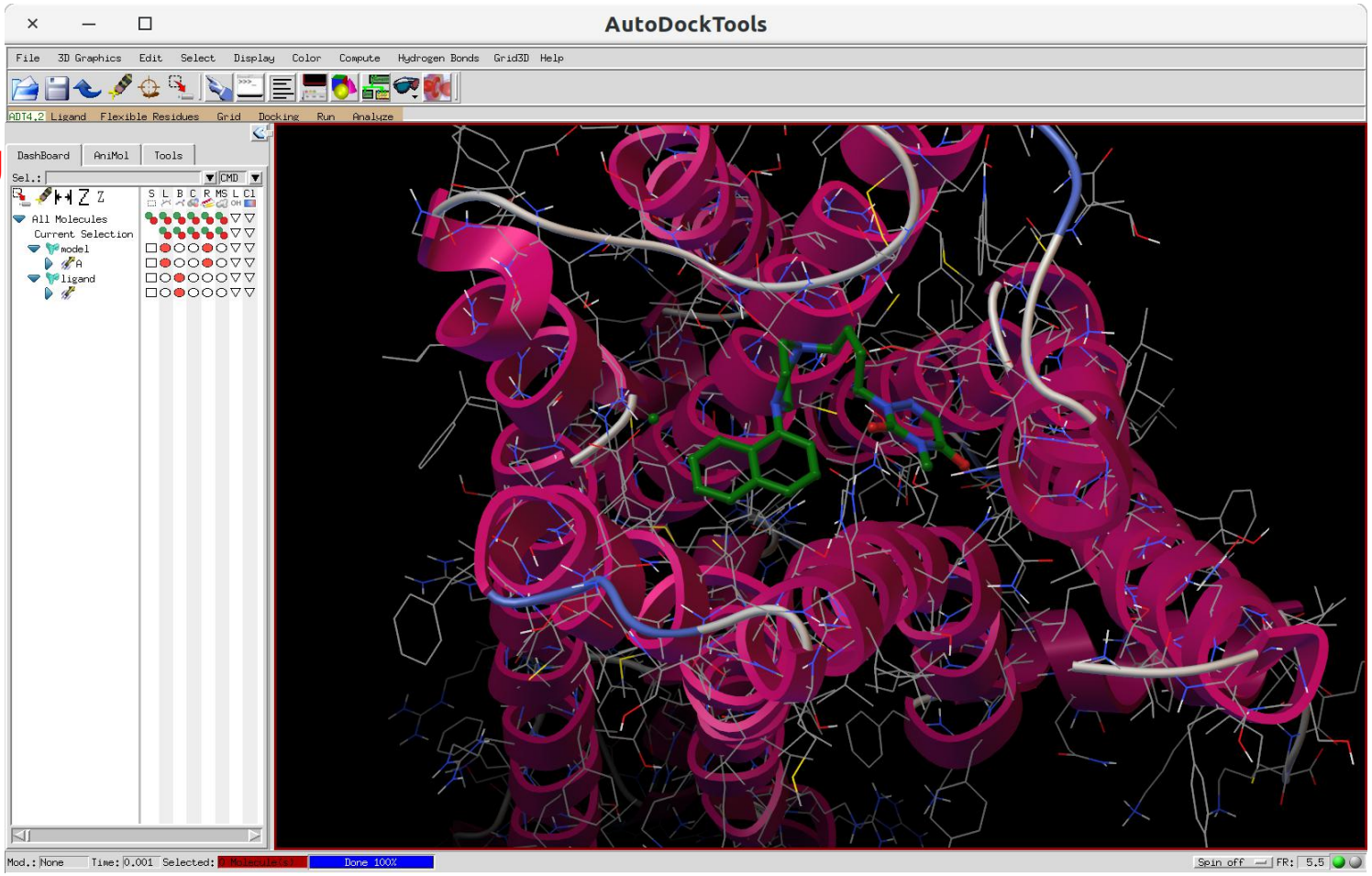
Molecular Docking with Autodock on BioHPC

 # Analysis

Analyze -> Docking -> Open -> dock.dlg

Analyze -> Conformations -> Load -> dock.dlg





Run on Your PC

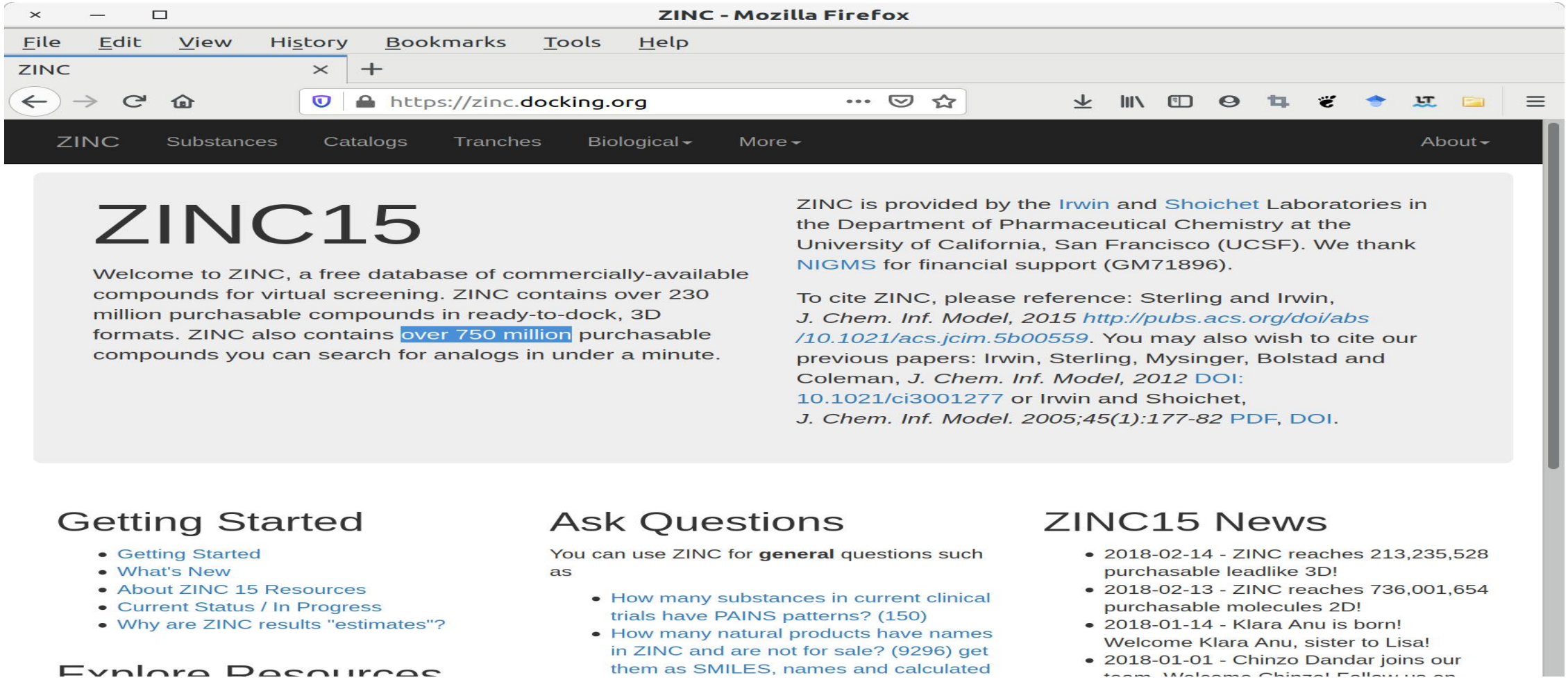
AutoDockTools

http://autodock.scripps.edu/downloads/resources/adt/index_html

AutoDock

http://autodock.scripps.edu/downloads/autodock-registration/autodock-4-2-download-page/

Virtual Screening



Thanks for your attention!

biohpc-help@utsouthwestern.edu